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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/591,279	06/09/2000	Katayoon Dehesh	15597/01/US	3330

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	12

DATE MAILED: 06/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/591,279	DEHESH ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-12 and 17-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Application Status

Claims 1-27 are pending in the application.

Amendment to the specification and claims 4-9, 11, and 12, addition of claims 17-27, receipt of a computer readable form of the sequence listing and a paper copy thereof in Paper No. 11 is acknowledged.

Claims 1-3 and 13-16 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

It is noted that the finality of the restriction requirement of Paper No. 5 was not stated in a previous Office action. Therefore, in order to clarify the record, the restriction requirement is still deemed proper and is therefore made FINAL.

Applicants' arguments filed in Paper No. 11 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Oath/Declaration

1. The objection to the oath or declaration as being defective is maintained. Applicants state that a substitute oath or declaration in compliance with 37 CFR 1.67(a) will be filed. However, as the substitute oath or declaration has not been received, the objection is maintained.

Claim Rejections - 35 USC § 112, Second Paragraph

2. Rejection of claims 4-12 and 17-27 under 35 USC 112, second paragraph, as being unclear due to the lack of a reference KAS polypeptide sequence is maintained. Applicants argue the claims have

been amended to recite a reference sequence of a native beta-ketoacyl-ACP synthase protein. Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

The claims remain indefinite because the specification provides many native beta-KAS amino acid sequences. As such, it is unclear as to which of the numerous beta-KAS sequences are meant to be included within the scope of the claims. In order to clarify the claims, it is suggested that, for example, applicants provide a specific reference sequence by reciting a specific SEQ ID NO:.

3. Claims 17 (claims 21-27 dependent therefrom), 18, and 19 (claim 20 dependent therefrom) are indefinite in the recitation of "alteration of the hydrophobic binding pocket". It is unclear from the claims and the specification as to applicants' intended alteration as the term can be interpreted as a change in the primary amino acid sequence of a protein or a change in the three-dimensional structure of a protein. Furthermore, as neither the specification nor the claims has provided a definition of "hydrophobic binding pocket", it is unclear as to the amino acid(s) of a beta-KAS that are to be included within the "hydrophobic binding pocket". It is suggested that applicants clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

4. The written description rejection of claims 4-12 and 17-27 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

Applicants argue that in accordance with the written description requirement, applicants need not disclose all things encompassed by the claims. Applicants argue the specification discloses the structure of the fatty acid/cerulenin binding pocket of the KAS protein, not limited to E. coli KAS II. Applicants argue the specification also discloses specific amino acids in the binding pocket that may be engineered to provide altered substrate specificity. Applicants argue that one skilled in the art would understand the disclosed structures are applicable to the amino acid sequences of Figure 12, which discloses a KAS amino acid sequence alignment of KAS proteins from plant, bacterial, mammalian, and other organisms. Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

As written, the claims fail to provide a sufficient description of the claimed genus of engineered beta-KAS proteins. The genus of engineered polypeptides of claims 4-7, 17, 18, 21-24, and 26 encompasses all beta-KAS polypeptides or all plant, prokaryotic, or E. coli beta-KAS polypeptides with any modifications or any modifications of the hydrophobic binding pocket that result in a beta-KAS protein with altered specificity for any substrate. The genus of engineered polypeptides of claims 4-7, 17, 18, 21-24, and 26 are described only by the functional features of the genus without providing any definition of the structural features of the species within the genus. The genus of engineered polypeptides of claims 8-12, 19, 20, 25, and 27 encompasses all engineered beta-KAS proteins with the recited modifications to any beta-KAS polypeptide or any plant, prokaryotic, or E. coli beta-KAS resulting in a beta-KAS protein with or without altered specificity. While it is acknowledged that claims 8-12, 19, 20, 25, and 27 recite particular amino acid residues for substitution(s), insertion(s), or deletion(s), this recitation fails to provide sufficient structural features of the claimed genus of engineered polypeptides such that a skilled artisan would recognize that applicants were in possession of the claimed invention. It is also acknowledged that the specification discloses KAS protein structures from several organisms including coordinates for the three-dimensional structure of the fatty acid/cerulenin binding pocket of the KAS protein.

The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of engineered proteins, the functional definition of the genus does not provide any or sufficient structural information commonly possessed by members of the genus which distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity

of the members of the genus. Therefore, the specification does not describe the claimed genus of engineered beta-KAS proteins such that a skilled artisan would recognize that applicants were in possession of the claimed invention.

5. The scope of enablement rejection of claims 4-12 and 17-27 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

Applicants argue the specification provides several KAS amino acid sequences and teaches a skilled artisan how to modify these sequences to produce the claimed polypeptides. Applicants argue the specification is not limited to disclosure of making only engineered E. coli KAS II proteins as the specification provides an amino acid sequence alignment of KAS proteins from various sources and additionally provides methods of analyzing and engineering KAS proteins in order to modify substrate specificities. Applicants argue the specification teaches in Examples 1 and 2 general principles of how a KAS II/cerulenin complex can be made and studied to identify amino acid residues that can be modified to affect KAS substrate specificity. Applicants argue the specification provides specific mutations of E. coli KAS II that result in altered substrate specificity and discloses ranges of mutations that can be engineered in plant KAS proteins with resulting altered substrate specificity. Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

It is noted that the claimed engineered polypeptides are not so limited to those amino acid sequences provided in Figure 12 as the claims are drawn to an engineered beta-KAS polypeptide from *any* source, *any* E. coli, *any* plant, or *any* prokaryotic source. The specification does not teach how to make all engineered beta-KAS polypeptides as encompassed by the claims. The specification, while providing general guidance for engineering any beta-KAS protein, provides only a single working example of specific mutations of a beta-KAS protein that retains KAS enzymatic activity, i.e., E. coli KAS II with the mutations as set forth in Figure 7 resulting in altered specificity for acyl-ACP. Methods of mutating a given amino acid sequence are well-known in the art, however, a skilled artisan would recognize that the resulting activity of a modified polypeptide is highly unpredictable and therefore, guidance is necessary to determine which mutations of a specific amino acid sequence result in maintaining and/or altering a

desired biological activity. While applicants have provided a method of generating a crystal structure for E. coli KAS II/cerelenin, a skiled artisan would recognize this structure will not be useful for determination of mutation(s) for *any* beta-KAS polypeptide from *any* source, *any* E. coli, *any* plant, or *any* prokaryotic source for a desired biological effect. As stated in a previous Office action, the specification does not support the broad scope of the claims because the specification does not establish: (A) regions of the KAS polypeptide structure of any organism which may be modified without affecting enzymatic activity and in regards to claims 4-7 and 17-27, altering substrate specificity; (B) the general tolerance of *any* KAS from *any* organism, *any* KAS from *any* prokaryotic or plant source or *any* KAS from E. coli to modification and extent of such tolerance as mutations of a polypeptide's amino acid sequence from one source, e.g., E. coli, will not necessarily have the same biological effect(s) in the corresponding enzyme from another source, e.g., plant, particularly in the case of E. coli KAS II and Cuphea pulcherrima KAS IV where the corresponding amino acids in the hydrophobic pocket are not identical (see for example page 29 and Figure 11 of the instant specification) and one of skill in the art would recognize the unpredictability as to whether similar mutations in C. pulcherrima KAS IV would maintain enzymatic activity and in regards to claims 4-7 and 17-27, altering substrate specificity; (C) the general tolerance of *any* E. coli KAS to modification and extent of such tolerance as mutations in E. coli KAS II will not necessarily have the same biological effect(s) in other E. coli KAS polypeptides, e.g., Moche et al. (J Biol Chem 274:6031-6034) dislcose that amino acid sequences for E. coli KASIII show very low degrees of sequence identities to E. coli KASI and KASII (page 6033, left bottom); (D) a rational and predictable scheme for modifying specificity of the co-substrate malonyl-ACP in *any* beta-KAS, *any* plant or prokaryotic beta-KAS, or *any* E. coli beta-KAS; (E) a rational and predictable scheme for mutating residues of *any* KAS from *any* organism, *any* prokaryotic or plant source, or E. coli other than residues 108, 111, 114, 133, 193, and 197 of wild-type E. coli KAS II with an expectation of obtaining the desired acyl-ACP substrate specificity; (F) the predictability that mutating residues 113, 138, and/or 203 of *any* E. coli KAS or E. coli KAS II or residues 115, 139, and/or 204 of *any* plant KAS will generate a KAS with the desired biological effect as applicants have not disclosed the effects of these mutations on *any* E. coli

KAS, E. coli KAS II, or *any* plant KAS; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

6. The rejection of claims 8 and 9 under 35 U.S.C. 103(a) as being unpatentable over Huang et al. (IDS reference; EMBO J 17:1183-91, hereafter referred to as "Huang") in view of Edwards et al. (IDS reference AO; FEBS Letters 402:62-6, hereafter referred to as "Edwards") is maintained. The rejection was fully explained in a previous Office action.

Applicants argue that there is no motivation to combine the references of Huang and Edwards. Applicants argue the examiner has applied an impermissible obvious-to-try standard. Applicants argue Applicants' position appears to be that Huang does not teach or suggest the function of the residues identified as active site residues and therefore, there is no motivation by Edwards to mutate these residues. Applicants argue the examiner's suggested motivation "is merely an exploration of a general approach that seems to be a promising field of experimentation". Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In this case, Edwards provides a clear motivation for combining the references as Edwards suggests mutating residues of E. coli KAS II to identify those residues involved in

catalysis (page 66, bottom right) - however, Edwards does not teach specific amino acids involved in catalysis. Huang teaches amino acids of the E. coli KAS II catalytic site, including positions 202, 205, 340, 349, 375, and 398-400 (pages 1186-1189), and at the time of the invention an ordinarily skilled artisan would have had the ability to generate such mutations. It is acknowleged that Huang does not provide specific functions for the specific amino acids identified by Huang as active site residues. However, given a specific amino acid sequence, i.e., E. coli KAS II, and specific residues involved in catalysis as determined by Huang, methods of analyzing active site residues by mutagenesis to determine the amino acids involved in catalysis were well known at the time of the invention, and an ordinarily skilled artisan would have been motivated to do so in view of Edwards' suggestion for mutating E. coli KAS II amino acids to determine those involved in E. coli KAS II catalytic activity. Therefore, the motivation provided by Edwards is clearly more than applicants' assertion that the examiner's provided motivation is an "exploration of a general approach that seems to be a promising field of experimentation". Thus, an E. coli KAS II polypeptide with mutations at positions 202, 205, 340, 349, 375, and/or 398-400 would have been *prima facie* obvious to one of ordinary skill in the art.

7. Rejection of claims 8-10 under 35 U.S.C. 103(a) as being unpatentable over Moche et al. (IDS reference AL; J Biol Chem 274:6031-34, hereafter referred to as "Moche") in view of Edwards. The rejection was fully explained in a previous Office action.

Applicants argue that there is no motivation to combine the references of Moche and Edwards. Applicants argue the examiner has applied an impermissible obvious to try standard. Applicants argue the examiner's suggested motivation "is merely an exploration of a general approach that seems to be a promising field of experimentation". Applicants' argument has been fully considered but is not found persuasive to overcome the rejection.

As previously stated, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In this case, Edwards provides a clear

motivation for combining the references as Edwards suggests mutating residues of E. coli KAS II to identify those residues influencing catalysis (page 66, bottom right) - however, Edwards does not teach specific amino acids that influence catalysis. Moche teaches amino acids of the E. coli KAS II substrate binding region, including residues G107, I108, L111, F 133, V134, I138, A162, A193, G198, F202, L342, and F400 (page 6032, middle right). Moche specifically suggests mutating glycine at position 107 to a serine (page 6033 bottom right). At the time of the invention an ordinarily skilled artisan would have had the ability to generate such mutations. Given a specific amino acid sequence, i.e., E. coli KAS II, and specific residues involved in substrate binding as provided by Moche, methods of analyzing active site residues by mutagenesis to determine the amino acids involved in substrate binding thus influencing enzymatic activity were well known at the time of the invention, and an ordinarily skilled artisan would have been motivated to do so in view of Edwards' suggestion for mutating E. coli KAS II amino acids to determine those involved in E. coli KAS II catalytic activity. Therefore, the motivation provided by Edwards is clearly more than applicants' assertion of an "exploration of a general approach that seems to be a promising field of experimentation". Thus, an E. coli KAS II polypeptide with mutations at positions 107, 108, 111, 133, 134, 138, 162, 193, 198, 202, 342, and/or 400 would have been *prima facie* obvious to one of ordinary skill in the art.

Conclusion

8. No claim is in condition for allowance. All claims are rejected.

Applicants' addition of claims 17-27 necessitated the new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 6:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

REBECCA E. PROUTY
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